Decision Memo for Abarelix for the Treatment of Prostate Cancer (CAG-00238N)

Decision Summary

The Centers for Medicare & Medicaid Services (CMS) has made the following determinations regarding the use of abarelix in the treatment of patients with prostate cancer.

1) Consistent with the specifications of the FDA labeling, the evidence is adequate to conclude that abarelix is reasonable and necessary as a palliative treatment in patients with advanced symptomatic prostate cancer in whom gonadotropin-releasing hormone (GnRH) agonist therapy is not appropriate, who decline surgical castration, and who present with one of the following:
(a) risk of neurological compromise due to metastases,
(b) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or
(c) severe bone pain from skeletal metastases persisting on narcotic analgesia.

Also consistent with the FDA labeling, the following additional conditions for coverage must be met to ensure that abarelix is used only in patients for whom the drug is indicated:

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- The patient has been evaluated and the drug has been prescribed by a physician who has attested to the following qualifications and accepted the following responsibilities, and on that basis, has enrolled in the post-marketing risk management program established by the drug manufacturer.

- The physician has attested willingness and ability to:

- Diagnose and manage advanced symptomatic prostate cancer;
- Diagnose and treat allergic reactions, including anaphylaxis;
- Have access to medication and equipment necessary to treat allergic reactions, including anaphylaxis;
- Have patients observed for development of allergic reactions for 30 minutes; following each administration of abarelix;
- Understand the risks and benefits of palliative treatment with abarelix;
- Educate the patients on the risks and benefits of palliative treatment with abarelix;
- Report serious adverse events as soon as possible to the manufacturer or the FDA.

2) The evidence is not adequate to conclude that abarelix is reasonable and necessary for indications other than that specified above. All other uses of abarelix therefore are not covered. In light of the concern regarding safety risks of abarelix, off-label uses that may appear in listed statutory drug compendia on which Medicare and its contractors rely to make coverage determinations will remain non-covered unless CMS extends coverage through a reconsideration of this NCD.

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Decision Memo

To: Administrative File: CAG #00238
Abarelix (Plenaxis™) for the Treatment of Prostate Cancer

From:

Steve Phurrough, MD, MPA
Director, Coverage and Analysis Group

Louis Jacques, MD
Director, Division of Items and Devices

Elizabeth Truong
Lead Analyst

Gay Burton
Analyst

Carlos Cano, MD
Lead Medical Officer

Subject: Coverage Decision Memorandum for Abarelix (Plenaxis™) for the Treatment of Prostate Cancer

Date: March 15, 2005

I. Decision

The Centers for Medicare & Medicaid Services (CMS) has made the following determinations regarding the use of abarelix in the treatment of patients with prostate cancer.

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- The physician has attested willingness and ability to:
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II. Background

Prostate cancer

An estimated 230,000 new cases of prostate cancer occurred in the United States during 2004. Prostate cancer incidence rates are significantly higher in black men than in white men. With 29,900 deaths projected in 2004, prostate cancer is the second leading cause of cancer death in men. The only well-established risk factors for this condition are age, race, and family history of the disease. This form of cancer is commonly diagnosed in North America and northwestern Europe and is rare in Asia and South America. More than 70% of all prostate cancer cases in the U.S. are diagnosed in men over age 65. Eighty-six percent of all prostate cancers are discovered in the local and regional stages and the five-year survival rate for patients whose tumors are diagnosed at these stages is close to 100%. Recent data indicate that the 10-year survival for all stages combined is 84%.[1]

Treatment options vary once the disease is diagnosed depending on age, stage of the cancer, and other individual medical conditions. Surgery (e.g., radical prostatectomy) or radiation is typically used for early-stage disease. Hormonal therapy, chemotherapy, and radiation (or combinations of these treatments) are used for more advanced disease. More recently, hormonal treatment has also been utilized as supplemental therapy for early-stage disease in younger, asymptomatic men with high-grade tumors. In men with disseminated disease, hormone treatment may control prostate cancer growth for long periods by shrinking the size of the tumor, thus relieving pain or other symptoms such as urinary obstruction. Careful observation without immediate active treatment ("watchful waiting") may be indicated for certain patients (e.g., elderly individuals with short life expectancy or less aggressive tumors.) [2]

Hormonal therapy

Prostate cancer is androgen-dependent. The reduction of circulating male hormones such as testosterone and dihydrotestosterone (DHT) results in clinically significant cancer remission and palliation. Thus, hormonal therapy has long been the mainstay of treatment for men with disseminated disease and has been considered palliative treatment for prostate cancer. As indicated above, since long-term disease-free survival in some patients has been extended many years, primary hormonal therapy is now increasingly considered an option for men with clinically localized disease. Nevertheless, the optimal form of hormonal treatment (i.e., time of initiation, appropriate duration, patient groups most likely to benefit) has not yet been established for this new use.

Bilateral orchiectomy was the first intervention to achieve androgen suppression in prostate cancer patients. An effective and efficient means to reduce serum testosterone concentrations, surgical castration has proven psychologically unacceptable for many men. The feminizing effects of diethylstilbestrol, an estrogen, also limited use of this form of medical (chemical) castration. In recent years, hormonal therapy has evolved from orchiectomy and estrogens to the use of synthetic drugs known as gonadotropin-releasing hormone (GnRH) agonists or analogues.[3] GnRH agonists include drugs such as leuprolide (Lupron™) and goserelin (Zoladex™). Over the course of a few days after treatment initiation, GnRH agonists suppress the production of testosterone and DHT, the main male hormones that stimulate primary prostate tumor and metastatic growth.

GnRH analogues are structurally similar to endogenous GnRH and have an affinity for the same pituitary cellular receptors but produce a different effect than the natural ligands. GnRH receptor agonists initially stimulate luteinizing hormone (LH) production more potently than natural GnRH, which in turn causes a drug-induced surge of testosterone and DHT generally lasting 14 to 21 days before inhibition of LH production, which ultimately results in the suppression of testosterone and DHT.[4]

The initial surge of male hormones can precipitate clinical symptoms in patients with locally advanced or metastatic prostate cancer. The “testosterone surge” has been linked with clinical worsening in some patients with advanced disease, a clinical “flare” manifested as increased pain from bone metastases, impaired urinary or renal function, and decreased neurological function (e.g., spinal cord or nerve root compression). In the first few weeks of hormonal treatment, signs or symptoms of a clinical flare due to a GnRH analogue-induced androgen surge may occur in advanced symptomatic patients and, depending on severity, may require surgical orchiectomy for management.

Antiandrogens such as flutamide (Eulexin™) or bicalutamide (Casodex™) are androgen antagonist drugs that tend to nullify the action of testosterone and DHT by binding to their cellular receptors without eliciting a physiological response. These drugs are thus often used in conjunction with GnRH agonists to limit the adverse clinical effects produced by the initial androgen surge in patients with advanced or symptomatic prostate cancer. [5] In addition, antiandrogens such as flutamide have been approved for use in combination with GnRH agonists but have also been used as monotherapy to minimize side effects of androgen deprivation therapy that cause significant morbidity (e.g., osteoporosis, anemia) or affect quality of life (e.g., impotence, fatigue, hot flashes). [6]

Abarelix

In contrast with GnRH agonists, newer compounds such as abarelix (Plenaxis™) are thought to be devoid of agonist activity and to lack an initial androgen-stimulating effect and are thus considered GnRH receptor antagonists. Clinical studies have indicated that these drugs block GnRH and inhibit LH production thereby suppressing testosterone and DHT production without the initial stimulation of LH and subsequent surge of testosterone or DHT.[7] Consequently, abarelix has been proposed as a substitute for GnRH agonists with and without antiandrogens in the treatment of patients with advanced prostate cancer for whom a surge in androgen blood levels may pose a risk of worsening symptoms ("clinical flare"). For this indication, abarelix is the first GnRH receptor antagonist to receive approval from the Food and Drug Administration (FDA).

However, immediate-onset systemic allergic reactions, some resulting in hypotension or syncope, have occurred after administration of abarelix. These immediate-onset reactions have been reported to occur following any administration of abarelix, including subsequent doses. The cumulative risk of such a reaction increases with the duration of treatment. For instance, in one of the clinical trials submitted by the manufacturer to the FDA for drug approval that included patients with advanced, symptomatic prostate cancer, 3 of 81 (3.7%) patients experienced an immediate-onset systemic allergic reaction within minutes of receiving abarelix.

Thus, for safety reasons, the FDA granted abarelix approval with marketing restrictions. The agency has required that following each injection of abarelix, patients should be observed for at least 30 minutes in the office and, in the event of an allergic reaction, managed appropriately. Only physicians who have enrolled in a post-marketing risk management program agreed-upon by the manufacturer and the FDA may prescribe abarelix based on their attestation of qualifications and acceptance of responsibilities required by the FDA.

In addition, the effectiveness of abarelix in suppressing serum testosterone to castration levels decreased with continued dosing in some patients. The drug labeling addresses this decrease of effectiveness with ongoing treatment and physicians are advised to measure serum total testosterone concentrations just prior to administration on Day 29 and every 8 weeks thereafter prior to administration of a new dose to assess the effectiveness of treatment. Effectiveness beyond 12 months has not been established.

III. History of Medicare Coverage

CMS has issued no previous national coverage determination (NCD) for abarelix.

On June 22, 2004, CMS accepted a NCD request from Praecis Pharmaceuticals, Inc., the manufacturer of Plenaxis™. The requestor asked specifically for an NCD on the use of Plenaxis™ (abarelix for injectable suspension) under the Medicare program. The formal request letter is available for viewing online at: http://www.cms.hhs.gov/mcd/viewtrackingsheet.asp?id=129.

Benefit Category Determination

Medicare is a defined benefit program. An item or service must fall within one or more benefit categories, and not otherwise be excluded by statute from coverage §1812 (scope of Part A); §1832 (scope of Part B); §1861(s) (definition of medical and other services). Abarelix is eligible for coverage under 1) §1861(b) of the statute when administered in an inpatient hospital setting, 2) §1861(s)(2)(A) when administered in a physician's office, and 3) §1861(s)(2)(B) when administered in an outpatient hospital setting.

IV. Timeline of Recent Activities

June 22, 2004 CMS accepts Praecis' request for a national coverage determination.

	Praecis' request and recommendations for coverage are available for review and comment. The initial 30-day public comment period begins with this acceptance date, and ends after 30 calendar days. CMS considers all public comments, and is particularly interested in clinical studies and other scientific information relevant to the technology under consideration as well as comments on the appropriate benefit categories to which the technology should be assigned.
August 13, 2004	Comments from the 30-day public comment period are available for viewing.
December 17, 2004	The proposed decision memorandum is available for public comment. Instructions for submitting comments are available at http://www.cms.hhs.gov/coverage/8h.asp
December 17, 2004 –January 16, 2005	Second 30-day public comment period extends through this period.
March 15, 2005	The final decision memorandum is posted.

V. FDA Status

Abarelix was first submitted to the FDA for approval in 2001 with a proposed target population of men with local, regional, or advanced carcinoma of the prostate where androgen suppression was appropriate. The FDA determined upon review that the risks of abarelix exceeded its benefits for the proposed target population and did not approve the original submission. Specifically cited were 1) the risk of serious allergic reactions, including anaphylaxis with hypotension and syncope, and 2) the risk of loss of efficacy over time. [8]

The manufacturer resubmitted an application on February 25, 2003 providing for the use of abarelix (injectable suspension, 100 mg) for the palliative treatment of men with advanced symptomatic prostate cancer in whom LHRH agonist therapy is not appropriate and who refuse surgical castration, and have one or more of the following: (1) risk of neurological compromise due to metastases, (2) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or (3) severe bone pain from skeletal metastases persisting on narcotic analgesia.

The resubmitted application narrowed the originally proposed indication to “use of the drug in a population for whom the benefits of the drug may outweigh the risks but in whom the drug can be safely used only if distribution and/or use is restricted.” The application also provided for a risk management program that would help ensure the safe use of abarelix in the approved indicated population.

After completing the review of the amended application, the FDA concluded that adequate information had been presented to approve the application for abarelix (injectable suspension, 100mg) with restrictions to ensure safe use under 21 CFR Part 314 Subpart H for the indication proposed in the resubmission. Accordingly, on November 25, 2003, the FDA approved marketing of this drug product with specific restrictions on distribution and use embodied in a risk management program agreed upon by the manufacturer.

The FDA considered the risk management program (Plenaxis Risk Management Program) an important part of postmarketing risk management for abarelix to “ensure distribution only to physicians with the training and experience necessary to assure safe use of the drug,” and to ensure use of abarelix “only in patients for whom the drug is indicated as set forth in the indications and usage section of the FDA-approved labeling.” The program includes the following components:

1. Enrollment of qualified physicians in a physician-prescribing program that ensures that abarelix is distributed only to these enrolled physicians and that the use of abarelix is in the approved indicated population.

2. Implementation of a program to educate physicians, hospital pharmacists, patients, and distributors about the risks and benefits of abarelix and responsibilities of being part of the prescribing program.

3.

Implementation of a reporting and collection system for serious adverse events associated with the use of abarelix

4.

Implementation of a plan to evaluate the effectiveness of the abarelix risk management program. 9

VI. General Methodological Principles

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member (§1862(a)(1)(A) of the Social Security Act.) The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve net health outcomes for patients. The general methodological principles of study design utilized in our review of the evidence are in Appendix B.

VII. Evidence

Introduction

When making national coverage determinations, CMS evaluates relevant clinical research studies to determine whether or not the evidence is of sufficient strength to support a finding that an item or service is reasonable and necessary. Methodologists have developed criteria to determine weaknesses and strengths of clinical research. In general, some of the methodological attributes of individual studies associated with stronger evidence include:

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- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Large enough sample sizes in studies to 1) make chance an unlikely explanation for what was found; and 2) demonstrate both statistically as well as clinically significant outcomes that can be extrapolated to the Medicare population.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm about the intervention and other psychological factors may lead to an improved perceived outcome by either the patient or assessor.
- The measures of clinical effectiveness are appropriate for the condition and include final outcomes such as reduced mortality or improved quality of life. In studies relying on intermediate (surrogate) outcomes, a strong and consistent association between the surrogate outcome and the final outcome has been demonstrated.

Consistent findings across studies of net health outcomes associated with a therapeutic intervention as well as the magnitude of its risks and benefits are also key consideration in the coverage determination process.

For this decision memorandum, CMS reviewed the available clinical evidence on the use of abarelix in advanced cancer of the prostate. CMS evaluated the individual published clinical studies provided by the requestor and searched for any additional relevant published articles to determine if using abarelix in the treatment of advanced prostate cancer improved health outcomes when compared with bilateral orchiectomy or other chemical testosterone ablation modalities such as GnRH agonists and antiandrogen drugs, which conform to the current standard of care for the affected population. We specifically sought any articles relevant to the following indication:

“The palliative treatment of men with advanced symptomatic prostate cancer in whom LHRH agonist therapy is not appropriate and who refuse surgical castration, and have one or more of the following: (1) risk of neurological compromise due to metastases, (2) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or (3) severe bone pain from skeletal metastases persisting on narcotic analgesia.”

Clinical investigators have utilized a variety of validated instruments and tests to assess quality of life for treated patients with prostate cancer. Quality of life measures are outcomes of interest for our review in addition to mortality rates, incidence of adverse events from treatment, or complications due to disease progression. With respect to the use of a drug like abarelix, we prefer studies where outcome measures are not limited to effects on intermediate outcomes (e.g., serum levels of testosterone) but include beneficial or adverse clinical effects of import to the patient such as improvement in pain or functional capacity and measures of survival such as overall, progression-free and cancer-specific survival.

The literature search was limited to comparative prospective studies including randomized and non-randomized controlled clinical trials. We did however include in the review a published study submitted by the requestor to and considered by the FDA that had no active control group and included only symptomatic subjects for whom alternative chemical castration was reportedly contraindicated.[10] In addition to our assessment of the clinical scientific literature, we reviewed and utilized the findings of the FDA medical review of safety and efficacy for abarelix, a document published by that agency and made available on its website.[11] CMS also requested information from experts and professional societies and sought available evidence-based practice guidelines, consensus statements, and position papers. The body of evidence reviewed in this decision memorandum contains no confidential or proprietary information submitted by the requestor to CMS.

Discussion of evidence reviewed

1. Assessment questions

The development of an assessment in support of Medicare coverage decisions is based on the same general question for almost all requests, i.e., “Is the evidence sufficient to conclude that the application of the technology under study will improve final health outcomes for Medicare beneficiaries?” The formulation of specific questions for the assessment recognizes that the effect of an intervention can depend substantially on how it is delivered, to whom it is applied, the alternatives with which it is being compared, and the delivery setting. In order to appraise the health outcomes of using abarelix for the treatment of invasive prostate cancer in comparison with other drug regimens, CMS sought to address the following questions:

- Does abarelix improve health outcomes of men with prostate cancer compared to standard medical therapy with GnRH agonists (e.g., leuprolide, goserelin) with and without antiandrogens (e.g., flutamide, bicalutamide)?

- What subgroups of patients with prostate cancer are likely to benefit from the new drug?

2. External systematic reviews/technology assessments

Systematic reviews are based on a comprehensive search of published studies to answer a clearly defined and specific set of clinical questions. A well-defined strategy or protocol (established before the results of the individual studies are known) guides this literature search. Thus, the process of identifying studies for potential inclusion and the sources for finding such articles is explicitly documented at the start of the review. Finally, systematic reviews provide a detailed assessment of the studies included.[12]

In our assessment, we seek to identify and appraise any available external systematic reviews focused on the medical technology under consideration. We found no systematic reviews on abarelix published in the peer-reviewed literature and available to CMS for this evaluation.

As mentioned above, we did rely on the published integrated review of safety and efficacy produced by the FDA. During the approval process, the FDA has access to the most comprehensive trial data available, some of which may be proprietary and may remain unpublished after agency approval. However, in this decision memorandum we only incorporate into our own summary and analysis of the evidence those FDA medical review findings and evaluation that are publicly available. [13]

3. Internal technology assessment

Literature search strategy

In addition to studies received from the manufacturer, CMS performed a search for any individual studies available on the effect of abarelix on patient outcomes through November 17, 2004. We defined the following inclusion and exclusion criteria for the selection of articles for this review.

- Studies would be comparative and prospective phase 3 trials
- Case series and case reports would be excluded
- Studies would include men with prostate cancer that received abarelix
- Studies would be reported in English

CMS queried the Medline database on August 5, 2004 and on November 17, 2004 for clinical trials evaluating the effect of abarelix using the following electronic search strategy.

- Prostate cancer AND (abarelix OR Plenaxis OR GnRH antagonist OR gonadotropin-releasing hormone antagonist)

Search results

The literature search yielded 22 citations for abstract review. Two articles met the inclusion criteria for full-text article retrieval and data abstraction. Both of these studies had been included in the packet submitted by the requestor to CMS. We sought to identify any additional relevant articles through manual search of references and through communications with the requestor and researchers in the field. Data from studies submitted to the FDA during the drug approval process that the requestor considered proprietary information remained unpublished during our review and were not part of the publicly available body of evidence and thus were not included in this national coverage analysis. We did however take into account the published observations of the FDA with respect to both published and unpublished studies included in the medical synthesis of the data on abarelix that was part of the approval package posted by the FDA on its website. [14]

Key data from the two full-text articles reviewed that reported on phase 3 controlled prospective trials and addressed the analytical questions posed by CMS were extracted and appear in evidence tables in the Appendix. As mentioned above, also included in the evidence tables is a published one-arm uncontrolled study of the population designated in FDA labeling.[15] In conjunction with data from the clinical review of the safety and efficacy of abarelix performed by the FDA, information contained in the evidence tables served as the basis for CMS' conclusions about the overall adequacy of the evidence to determine under what conditions abarelix would be considered reasonable and necessary.

The following section summarizes the results of our review and that of the FDA on the use of abarelix in the treatment of prostate cancer. Studies are grouped for discussion under each assessment question. The two controlled studies discussed under the first question and the one-arm study addressing the patient group most likely to benefit from the drug constitute three of the four studies the FDA considered primary in support of the efficacy and safety of abarelix.

Does abarelix improve health outcomes of men with prostate cancer compared to standard medical therapy with GnRH agonists (e.g., leuprolide, goserelin) with and without antiandrogens (e.g., flutamide)?

Two studies that met our inclusion criteria addressed this question.[16] These published studies involved men with less advanced prostate cancer than the symptomatic patients comprised in the approved indication. The purpose of the two randomized, open label, active comparator-controlled, and multicenter studies was to assess the safety and the pharmacodynamic effectiveness (i.e., suppression of serum testosterone to less or equal than 50ng/dL without initially inducing a testosterone surge) in prostate cancer patients who did not have advanced symptomatic disease.

Patients were randomized 2:1 to treatment with abarelix or the active comparator leuprolide in the study by McLeod et al. and leuprolide plus bicalutamide in the study by Trachtenberg et al. All patients assigned to treatment with abarelix received 100 mg by IM injections on days 1, 15, 29, and every 28 days thereafter. Treatment periods were 6 months or 12 months depending on the study protocol with all abarelix patients having the option to continue treatment.

Both studies utilized similar outcome measures. Given acceptance by the FDA that "attainment of castration concentrations of testosterone by day 29 and maintenance of these levels through at least 3 dosing cycles" was a surrogate efficacy endpoint for GnRH agonists, the following pharmacodynamic efficacy endpoints were established for these studies:

1. Achievement and maintenance of serum testosterone concentrations of equal or less than 50 ng/dL from study day 29 through day 85
2. Avoidance of testosterone surge, i.e., no serum testosterone surge between study days 2 and 8 exceeding baseline measurement by 10% or greater
3. Rapidity of medical castration, i.e., defined as ability to achieve serum testosterone of equal or less than 50ng/dL by study day 8. [17]

Successful outcome in each clinical trial required that, 1) abarelix not be inferior to treatment with the active control for endpoint 1 and, 2) abarelix be superior to treatment with the active control for endpoints 2 and 3.

Pharmacodynamic efficacy results. Medical castration levels (serum testosterone concentration at or below 50 ng/dL) were achieved and maintained at day 85 by 91.7% (Trachtenberg et al.) and 92.9% (Mc Leod et al.) of the abarelix patients and 95.5% and 95.2% of the active control patients respectively in the two controlled clinical trials reviewed by CMS.[18] No patients in the abarelix treatment groups (0 of 348) across the two studies combined experienced a testosterone surge while 84% of patients (144 of 172) in the active control groups experienced a surge. No patients in the active control group were medically castrate on day 8 whereas 24%, 56%, and 70% of patients on abarelix combined across studies had serum testosterone concentrations equal or less than 50 ng/dL at 2, 4, and 8 days respectively.

Safety. The following are general safety findings from the three primary, controlled safety studies (including the studies by McLeod et al. and Trachtenberg et al.) excerpted verbatim from the FDA medical review:

“During clinical trials with abarelix, three safety issues of concern were identified: immediate systemic allergic reactions, hepatic toxicity, and prolongation of the QT interval.

1) Immediate onset systemic allergic reactions (occurring within 30 minutes of dosing), were observed in 1.1% (15/1397) of patients dosed with abarelix across clinical trials. In 14/15 patients who experienced an allergic reaction, each developed symptoms within 8 minutes of injection. The cumulative rates for an allergic reaction on days 56, 141, 365, and 676 were 0.51%, 0.80%, 1.24% and 2.91% respectively. Seven (7) patients experienced hypotension or syncope as part of their allergic reaction, representing 0.5% of all patients. The cumulative rates for these types of reactions on days 56, 141, 365, and 617 were 0.22%, 0.32%, 0.61%, and 1.67% respectively. No immediate-onset systemic allergic reactions occurred in the active comparator groups.

2) A greater proportion of patients treated with abarelix in the controlled safety trials had an increase in serum transaminase levels (particularly alanine aminotransferase or ALT) than patients treated with leuprolide or leuprolide plus bicalutamide. A small percentage of these increases were of clinical significance in both groups. The percentages of abarelix-treated patients reporting serum ALT values > 2.5 times upper limit of normal or > 200U/L were 8.2% and 1.8% respectively (compared to 6.6% and 1.1% respectively in the active comparator groups combined.) [19]

3) Treatment with either abarelix or active comparator prolonged the QT interval by >10 msecs from baseline."

What subgroups of patients with prostate cancer are likely to benefit from the new drug?

Koch et al. studied the response to treatment with abarelix of 81 men with advanced prostate cancer symptoms in an open label, single arm (abarelix only) multicenter study. Patients were enrolled if they had bone pain from skeletal metastases, retroperitoneal adenopathy causing ureteral obstruction, impending neurologic compromise, or an enlarged prostate gland or pelvic mass causing bladder neck outlet obstruction. The primary purpose of the trial was to demonstrate that patients with advanced symptomatic prostate cancer could avoid bilateral orchiectomy through the first 12 weeks of treatment. This is the period when signs or symptoms of a clinical flare due to a GnRH-induced testosterone surge would occur and might require surgical orchiectomy for management.

Efficacy. Seventy (70) of the 72 (97%) men remained in the study and did not require orchiectomy through days 29 and 85. Two (2) patients were withdrawn before day 85 for treatment-related adverse events, specifically immediate-onset systemic allergic reactions. Medical castration was achieved in 57/72 patients (79%) on day 8, and in 96%, 97%, and 93% on days 29, 85, and 169, respectively. Although the study was not designed to assess specific clinical outcomes, none of the patients with bone metastases developed neurological symptoms, a majority of patients with a bladder drainage catheter had the catheter removed by 12 weeks, and a majority of patients with pain due to skeletal metastases were able to reduce the potency, dose, or frequency of narcotic analgesia by week 12.

Safety. Excluding premature withdrawals due to disease progression (N=10) and deaths (N=6), 3 of 81 patients (4%) were withdrawn prematurely because of a systemic allergic reaction that occurred within minutes of dosing on days 15 (urticaria), 29 (urticaria and pruritus), and 141 (syncope and hypotension), respectively. Among patients with baseline ALT values that were not greater than the upper limit of normal (ULN) at baseline, 25 of 75 (33%) had increases to values greater than ULN while on treatment; two patient had ALT elevations to levels 2.5 times greater than ULN.[20]

4. Medicare Coverage Advisory Committee

The Medicare Coverage Advisory Committee was not convened to review this issue.

5. Evidence-based Guidelines

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- Citations from the available drug compendia identified in §1861(t)(2)(B)(ii)(I) of the statute, the American Hospital Formulary Service-Drug Information (AHFS-DI) and the United States Pharmacopoeia-Drug Information (USP-DI), are listed below. [21]
- *AHFS-DI (2004)*
  "Abarelix is used for the palliative treatment of advanced symptomatic prostate cancer when GnRH agonist therapy is not appropriate, orchiectomy is unacceptable to the patient, and one or more of the following risk factors and/or clinical manifestations are present: risk of neurological compromise secondary to metastases; ureteral or bladder outlet obstruction secondary to local encroachment or metastatic disease; or severe bone pain from skeletal metastases that persists despite opiate analgesia."
- *USP-DI (2004)*
  "Carcinoma, prostate—Abarelix is indicated for palliative treatment of men with advanced symptomatic prostate cancer, in whom LHRH agonist therapy is not appropriate and who refuse surgical castration, and have one or more of the following: risk of neurological compromise due to metastases; ureteral or bladder outlet obstruction due to local encroachment or metastatic disease; or severe bone pain from skeletal metastases persisting on narcotic analgesia."

An on-line search of national cancer and professional society websites found no evidence-based practice guidelines addressing GnRH antagonists in the management of patients with advanced prostate cancer. For instance, both the National Comprehensive Cancer Network (NCCN) clinical practice guidelines for prostate cancer as well as the recommendations issued by the American Society of Clinical Oncology (ASCO) for the initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer, specifically discuss generally accepted treatment protocols and include recommendations for hormonal therapy in prostate cancer. Neither of these practice guidelines address treatment with GnRH antagonists.[22]

6. Professional Society Position Statements

The American Society of Clinical Oncology (ASCO) recommends “bilateral orchiectomy or medical castration with luteinizing hormone releasing hormone (LHRH) agonists for initial treatments of metastatic prostate cancer. A full discussion between practitioner and patient should occur to determine what is best for the patient (…). The patient needs to appreciate that there is a small potential gain in overall survival with the addition of a nonsteroidal antiandrogen to medical or surgical castration and that increased side effects may occur as a result.”[23]

7. Expert Opinion

Except from communications with the NCD requestor, CMS received no formal expert opinion statements from the medical or scientific community regarding this issue.

8. Public Comments

CMS received one comment during the first 30-day public comment period from the medical director of a local Medicare contractor. The commenter supported the NCD review, suggesting that CMS consider developing a NCD review addressing all drugs classified as gonadotropin releasing hormone (GnRH) analogues, e.g., Zoladex™ and Lupron™.

In the second 30-day comment period CMS received two comment submissions regarding the proposed decision memorandum, one from a manufacturer of a GnRH analogue, the other from the manufacturer of abarelix (Plenaxis™).

The first commenter supported the NCD's narrow focus on abarelix (Plenaxis™) rather than a review addressing all drugs classified as GnRH analogues.

The second commenter, the requestor of the current NCD, proposed that CMS cover abarelix (Plenaxis™) in practical clinical trials approved by CMS. CMS has opened a public dialogue on coverage and its relationship to data generation and recently held an Open Door Forum on February 14, 2005 to solicit public comment on the topic. CMS is developing a guidance document to clarify the process by which the practical clinical trial policy will be applied in the future and will continue to seek public input. We believe that coverage for clinical trials for abarelix (Plenaxis™) is best addressed in the larger context of this agency initiative rather than in this NCD.

We considered and incorporated into the final decision memo where appropriate a number of factual clarifications related to abarelix (Plenaxis™) and the management of prostate cancer proposed by the requestor in submitted comments. Some requested changes however were not incorporated in the final document. For instance, although the requestor questioned the characterization of “hepatic toxicity” in the proposed decision memo, this language was part of a paragraph excerpted verbatim from the FDA review. Furthermore, we could not include data cited by the requestor comparing elevations of transaminases that occurred with abarelix and active comparator agents since such data were not publicly available. Also we could not accept a review of the clinical effectiveness of abarelix (Plenaxis™) submitted by the manufacturer as a “systematic review” since it did not meet the generally accepted qualifying criteria (e.g., clear research or assessment question, explicit literature search strategy, article inclusion and exclusion criteria, uniform presentation of data, etc.) [24]

Finally, although the commenter questioned as imprecise wording the use of the term “serious” in reference to the side effects of abarelix (Plenaxis™), the reviews by FDA and CMS suggest that hypersensitivity reactions are serious relative to other hormonal therapy modalities. The FDA would not have instituted a post-marketing surveillance program with marketing restrictions and CMS would not have restricted coverage of off-label use if these agencies had not separately arrived at that considered judgment.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations made by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be “reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.” § 1862(a)(1)(A). This section presents the agency’s evaluation of the evidence considered and conclusions reached for the assessment question. It includes an appraisal of the effects of abarelix, a GnRH antagonist, on the health outcomes of Medicare beneficiaries compared to the current standard of care in hormonal therapy for patients with advanced prostate cancer, which includes GnRH agonists with or without antiandrogens.

Clinical considerations

The clinical relevance of the increase in testosterone in the first few weeks after administration of a GnRH agonist has been a matter of debate since these drugs were introduced into clinical practice. No studies have yet shown that the avoidance of an initial testosterone increase translates into any meaningful benefit for the majority of men with prostate cancer.

However, the specialty practitioner community appears to be in general agreement that there is a potential for an adverse effect from the testosterone surge in prostate cancer patients who have impending neurological compromise or symptoms such as severe bone pain. Expert clinicians also agree that additional administration of antiandrogens provides some protection from this initial testosterone flare.[25] It is unclear if the therapeutic value of combined hormonal therapy with GnRH agonists and antiandrogens in this population is only in blunting the effect of the testosterone flare (in which case there would be no need to continue antiandrogens beyond the first month of treatment since the overall effect on survival of combined androgen blockade is considered of negligible clinical importance). [26]

Beyond avoidance of testosterone surge and possible clinical flare, the utility of a hormonal therapy product in patients with prostate cancer will depend on 1) the ability of the drug to maintain chemical castration levels with long-term administration and 2) the occurrence of any unique side effects. In this instance, the higher frequency of immediate onset systemic allergic reactions from abarelix compared to that of GnRH agonists and uncertainty about its long-term endocrinologic efficacy raise concerns regarding its use for patients other than the population with disseminated symptomatic prostate cancer indicated in the FDA labeling. The precautionary measures built into the post-marketing risk management program agreed upon by the manufacturer and the FDA and the advanced stage with the associated reduced life expectancy in that subset of patients justify the use of abarelix for the indicated population.

Does abarelix improve health outcomes of men with prostate cancer compared to standard medical therapy with GnRH agonists (e.g., leuprolide, goserelin) with and without antiandrogens (e.g., flutamide)?

FDA Appraisal

Safety. In accordance with the general safety findings from the controlled clinical trials cited in the evidence section above, the FDA concluded that: “1) immediate-onset systemic allergic reactions occurring within 30 minutes of dosing in patients exposed to abarelix justify that patients be observed for at least 30 minutes after each injection of abarelix by a physician capable of treating a severe systemic allergic reaction, 2) the effects of abarelix on the liver should be addressed in labeling and require periodic monitoring of serum transaminase levels, 3) physicians should carefully consider whether the risks of abarelix treatment outweigh the benefits in patients with baseline QT interval values higher than 450 msec.”

Effectiveness.Based on criteria prospectively established with the sponsors that testosterone levels would not exceed a castration level threshold above 50 ng/dL in two consecutive measurements during the first twelve weeks of the study, the FDA considered abarelix non-inferior to the comparator treatment. They noted however that one of the three randomized controlled studies reviewed (which was not subsequently published) failed closely to meet this criterion. The FDA also expressed concern that failure to maintain suppression could become more apparent over time. Specifically, when suppression was considered through the end of the study (e.g., days 169 and 365), the effectiveness of abarelix steadily declined while that of the comparator was sustained. [27]

The FDA granted superiority to abarelix with regards to the two other agreed-upon endpoints, i.e., avoidance of testosterone surge and more rapid attainment of medical castration. Specifically, across both studies summarized in this decision memorandum, no patients (0 of 348 combined subjects) in the abarelix treatment groups experienced a testosterone surge while 84% of patient in the control groups (GnRH agonist without antiandrogen treatment) experienced a surge ($p<0.001$). Across studies combined, 70% of patients receiving abarelix were medically castrate on day 8 whereas none in the control groups had testosterone levels beneath the pre-defined threshold.

Thus, based on the evidence presented by the sponsor, the FDA considered abarelix for injectable suspension, in contrast to GnRH agonist, a “true GnRH antagonist that is devoid of LH and FSH releasing activity” and consequently “able to reduce serum testosterone to castrate levels without an initial antecedent surge.” The FDA agreed that abarelix could therefore provide significant clinical benefit for the hormonal management of men with advanced symptomatic prostate cancer and recommended that abarelix be approved for the palliative treatment of this group of patients in certain clinical conditions. However, for men with less severe prostate cancer, the FDA believed that “the potential benefits of treatment with abarelix *do not* outweigh the risks of treatment.” It was also recommended that approval of abarelix be contingent upon the sponsor’s implementing and maintaining a comprehensive risk management program with specified components and that a number of phase 4 studies be conducted. [28]

CMS appraisal

Only one of the two randomized controlled trials on abarelix included as a comparator intervention the clinically relevant treatment regimen for patients with prostate cancer for whom a testosterone surge is a concern when initiating hormonal therapy. Antiandrogens have long been shown to prevent or reduce the adverse consequences such as worsening bone pain of the GnRH agonist-induced transient rise in plasma testosterone levels in men with advanced prostate cancer. Addition of an antiandrogen to the GnRH analogue is considered standard care in these instances.[29]

In addition, both phase 3 controlled trials utilized surrogate (endocrinological and biochemical) outcomes as primary endpoints. Laboratory measurements of serological hormones and markers such as prostate-specific antigen (PSA) were used as a substitute for clinical endpoints measuring directly how patients felt, functioned, or survived.[30] Changes induced by abarelix on pharmacodynamic parameters were presumed to correlate with and predict health outcomes experienced by these patients.

Changes in laboratory values that a patient does not sense directly may be seen as links in the chain between an intervention and improved survival or perceived health. When the pathophysiology of a disease and the mechanism of action of a drug are well understood, it may be possible to link specific biologic or pharmacologic effects to a strong likelihood of improved health outcomes. In this instance, attainment of castrate levels of serum testosterone concentration (≤ 50 ng/dL) has long been considered an intermediate goal of hormonal therapy for prostate cancer. Consequently, in the application for abarelix and prior applications for GnRH agonists, the FDA accepted as a surrogate efficacy endpoint attainment by day 29 and maintenance of a serum testosterone at or below 50 ng/dL through at least three dosing cycles.

However, plausible beneficial phamacologic effects do not necessarily correlate with clinical benefit. The reasons for the absence of an expected correlation between pharmacologic and clinical effects are diverse. For instance, more than one disease pathway may affect final health outcomes in disease processes such as prostate cancer. Also, a drug may have other pharmacologic effects in addition to that being measured and thought to be beneficial.

In light of the serious side effects observed with the use of abarelix (the risk of which increases over time in the treated population), attainment of medical castration for three cycles may be an insufficiently validated surrogate endpoint in appraising the benefit of continued use of this drug. Concerns that the intervention has an unintended mechanism of action that is independent of the effect on hormone serum levels cast doubt on the ability to predict actual clinical effects solely on the basis of pharmacodynamic activity, particularly in patients expected to receive treatment for an extended period.[31]

CMS therefore concurs with the appraisal by FDA based on the concerns about safety and long-term efficacy raised by the studies available on abarelix. Given these concerns and other methodological questions regarding the appropriate comparator interventions and outcome measures, CMS considers the evidence inadequate to conclude that use of abarelix in patients with less severe prostate cancer than those with advanced symptomatic disease described in the FDA-approved indication is reasonable and necessary given the currently available alternative therapies for this condition. Nevertheless, recent data suggesting that follicle-stimulating hormone (FSH) may be an independent growth factor in prostate cancer and that abarelix may decrease FSH more efficaciously than GnRH agonists with or without antiandrogens indicate that abarelix may have a role in the treatment of men with hormone-responsive or resistant disease if additional confirming data become available.[32]

The serious concerns about the safety of abarelix also raise questions about the risk/benefit ratio for this drug in a variety of potential indications for which the evidence is substantially more limited than that available for prostate cancer. Therefore, additional clinical evidence showing improved net health outcomes for patients must support dissemination of abarelix to off-label indications for which GnRH agonists may be currently used or to future indications that are theoretically feasible for GnRH antagonists. Such off-label indications include but are not limited to assisted reproduction, endometriosis, leiomyoma, and breast cancer in women, benign prostatic hypertrophy in men, and central precocious puberty in children.[33]

What subgroups of patients with prostate cancer are likely to benefit from the new drug?

The initial, temporary (one or two weeks) rise in serum testosterone level may cause a worsening of prostate cancer symptoms known as “clinical flare” in men with advanced disease (i.e., patients with local encroachment or metastatic disease). Most commonly, the immediate consequence of this initial increase in circulating testosterone levels in men with metastatic disease is an increase in bone pain. More serious adverse events can occur less frequently including ureteral or bladder neck outlet obstruction, spinal cord compression and paralysis, and rarely, death. For this reason, as mentioned above, concomitant antiandrogen therapy (e.g., flutamide) is usually administered during at least the first month of treatment when GnRH agonists are used to treat men with advanced symptomatic prostate cancer. Antiandrogens may produce their own side effects though and may not completely block the potential adverse consequences of a testosterone surge.

The open label, single arm 24-week study by Koch et al. was the only one among those reviewed that enrolled and looked at the response of men with advanced, symptomatic prostate cancer. No other study available for CMS review compared health outcomes for patients with advanced symptomatic disease treated with abarelix with those for similar patients receiving the commonly used combination of a GnRH agonist and antiandrogen. The ability to draw firm conclusions about the observed beneficial effects of abarelix (e.g., avoidance of surgical castration during the first few weeks after initiation of treatment or noticeable sign and symptom alleviation) is thus limited by the lack of a comparison group in the single-arm trial that studied the population designated in the labeling. Non-comparative clinical trials cannot account for placebo effects.

Nonetheless, avoidance of orchiectomy for 12 weeks could be seen as indirect evidence that treatment with abarelix did not induce a clinically serious testosterone flare in the studied population.[34] Similarly, although the extent of a placebo effect cannot be ascertained, the treatment intervention resulted in a clinically significant decrease in pain intensity and other symptom relief in a number of patients. Also, this group of subjects with androgen-dependent advanced disease arguably represents a small sub-population of prostate cancer patients. The relatively low prevalence of the condition together with a low life expectancy may make it difficult to conduct a controlled trial with a regimen of GnRH agonist combined with antiandrogen as active comparator.

As noted earlier, the available randomized controlled studies comparing abarelix with currently utilized treatment regimens were limited to patients with asymptomatic disease. A temporary testosterone surge is not generally considered clinically significant in the management of these patients. We also noted that the primary endpoints of both published phase 3 controlled studies under review were limited to surrogate or intermediate outcomes (e.g., pharmacodynamic effects such as rapidity in achieving and ability to maintain a reduction in testosterone levels) rather than final health outcomes (such as bone pain or urinary obstruction). However, the ability of a GnRH antagonist such as abarelix to rapidly reduce serum testosterone levels without an initial increase in hormone concentration lends biological plausibility to the preferred use of this drug for the relatively small proportion of patients with advanced symptomatic disease. Although not contraindicated, use of GnRH agonists in these patients, particularly when not combined with an antiandrogen, can be problematic. The seriousness of the condition and the need for symptomatic relief in these patients together with the avoidance of a testosterone surge may outweigh concerns about immediate hypersensitivity reactions or hypotension and syncope if an expert practitioner able to manage these untoward effects performs the drug administration.

The risk-benefit ratio for the indicated use appears to differ substantially in another respect from that likely to face patients and practitioners if abarelix were to be used in earlier, less severe phases of prostate cancer or in other disease conditions. Abarelix has not demonstrated sustained efficacy even as assessed by serum testosterone levels alone. In fact, in one large study reviewed by the FDA, abarelix was marginally inferior to leuprolide in the percentage of patients who achieved and maintained medical castration as early as in weeks 4 through 12.[35] With efficacious drugs available in the market, and until additional data show the sustained efficacy of abarelix, its use for chronic conditions including but not limited to asymptomatic prostate cancer is not warranted. However, the concern of continuous efficacy over time is tempered if the drug is used for the palliative treatment of patients with advanced prostatic disease at risk for potentially serious symptom worsening associated with testosterone surge given the lower life expectancy associated with disseminated symptomatic disease.

Thus, the available evidence is adequate to conclude that abarelix meets a need for the sub-population of patients designated in FDA labeling, who may otherwise require surgical castration for the management of sign and symptom worsening associated with GnRH agonist-induced transient testosterone surge.

Conclusion

The Centers for Medicare & Medicaid Services (CMS) has made the following determinations regarding the use of abarelix in the treatment of patients with prostate cancer.

1) Consistent with the specifications of the FDA labeling, the evidence is adequate to conclude that abarelix is reasonable and necessary as a palliative treatment in patients with advanced symptomatic prostate cancer in whom gonadotropin-releasing hormone (GnRH) agonist therapy is not appropriate, who decline surgical castration, and who present with one of the following:
(a) risk of neurological compromise due to metastases,
(b) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or
(c) severe bone pain from skeletal metastases persisting on narcotic analgesia.

Also consistent with the specifications of the FDA labeling, the following additional conditions for coverage must be met to ensure that abarelix is used only in patients for whom the drug is indicated:

-
- The patient has been evaluated and the drug has been prescribed by a physician who has attested to the following qualifications and accepted the following responsibilities, and on that basis, has enrolled in the post-marketing risk management program established by the drug manufacturer.
- The physician has attested willingness and ability to:
    - Diagnose and manage advanced symptomatic prostate cancer;
    - Diagnose and treat allergic reactions, including anaphylaxis;
    - Have access to medication and equipment necessary to treat allergic reactions, including anaphylaxis;
    - Have patients observed for development of allergic reactions for 30 minutes; following each administration of abarelix;
    - Understand the risks and benefits of palliative treatment with abarelix;
    - Educate the patients on the risks and benefits of palliative treatment with abarelix;
    - Report serious adverse events as soon as possible to the manufacturer or the FDA.

2) The evidence is not adequate to conclude that abarelix is reasonable and necessary for indications other than that specified above. All other uses of abarelix therefore are not covered. In light of the concern regarding safety risks of abarelix, off-label uses that may appear in listed statutory drug compendia on which Medicare and its contractors rely to make coverage determinations will remain non-covered unless CMS extends coverage through a reconsideration of this NCD.

Appendix A. Evidence Tables [PDF, 59KB]

APPENDIX B

General Methodological Principles of Study Design

(Section VI of the Decision Memorandum)

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve net health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.

- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies

- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess net health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

In general, an intervention is not reasonable and necessary if its risks outweigh its benefits. Among other things, CMS considers whether reported benefits translate into improved net health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

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